EXHIBIT 5

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BY HAND DELIVERY

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Rm. 1-23
12420 Parklawn Drive
Rockville, Maryland 20857

Re: Docket Number 2005P-0127

Dear Madam or Sir:

The undersigned, on behalf of Aventis Pharmaceuticals Inc. ("Aventis"), a member of the sanofi-aventis Group, submits this reply to the comments of Kali Laboratories, Inc. (Kali) and Olsson, Frank and Weeda, P.C. (Olsson) on Sanofi's March 31, 2005 citizen petition (Docket Number 2005P-0127). That petition requested that if an ANDA applicant is not seeking approval of a 100 mg leflunomide tablet that is bioequivalent to Arava® (leflunomide) 100 mg tablets, that FDA require the applicant to perform *in vivo* bioequivalence testing to confirm that five of its 20 mg tablets are bioequivalent to one Arava® 100 mg tablet.

As an initial matter, we must respond to Olsson's unfounded allegation that we have failed to disclose relevant unfavorable information to the Agency. The allegation is false. First, contrary to Olsson's assertions otherwise, the 100 mg Arava tablet has remained continuously available since the date of approval. ("How Supplied" section of the Arava labeling entries in 2000 through 2005 editions of the PDR, Attachment A). The document produced by Olsson was simply a notice to the trade that the 100 mg tablet was no longer available through pharmacists. That the 100 mg tablet is no longer sold in a trade pack -- but is instead made available to physicians as a sample initiation dose -- is simply irrelevant for purposes of our petition.

Second, Olsson's comment is premised entirely on misinformation: "information in the public domain showing that Aventis discontinued 100 mg Arava tablets over three years ago." (Olsson comment at 2). Aventis has never discontinued the 100 mg Arava tablet. Rather, in January 2002, Aventis discontinued the 100 mg trade package. (Attachment B). Although Aventis stopped selling the 100 mg tablet, it did not stop manufacturing or marketing the 100 mg tablet. Since January 2002, Aventis has made the 100 mg tablet available as a "Physician Starter Sample." The company's www.arava.com website contains a link where doctors can request initiation doses of Arava. (Attachment C). Since 2002, Aventis has distributed more than 200,000 100mg Starter Packs for use by new patients.

That Olsson's client received a letter from the Office of Generic Drugs stating that the "100 mg strength has been discontinued from the market" does not mean that Aventis in fact discontinued the 100 mg Arava tablet. Aventis made no submission to the Agency to withdraw the product. To the contrary, Aventis has paid the drug product fee for the 100 mg tablet each year since the discontinuation of the trade pack. (Attachment D). It appears that FDA had briefly and mistakenly concluded that the product was withdrawn based upon Aventis's "Dear Pharmaceutical Buyer" letter. Aventis became aware of this mistake when the 100 mg tablet was moved to the discontinued products section of the 2004 edition of the Orange Book. (Attachment E). Afterwards, Aventis contacted the Agency and explained that the product was still available as a starter sample for physicians. (Attachment F). In response, FDA confirmed that such sampling falls within the ambit of marketing and advised Aventis to write the Orange Book staff to request that the 100 mg tablet be placed back on the approved drug products list. (*Id.*). The mistake was thus corrected in Cumulative Supplement 7 of the 2004 Orange Book. (Attachment G). The 100 mg tablet is currently and properly listed as a reference listed drug. (Attachment H). The Orange Book accurately reflects that Arava 100 mg tablets are available both for use as a loading dose and for purposes of bioequivalence testing. Because the 2005 Orange Book is available on FDA's website it is surprising that Olsson neglected to mention this in its comment.

FDA previously determined that bioequivalence data are a prerequisite to approval of five of 20 mg tablets as a substitute for the 100 mg loading dose. Without data establishing that five of their 20 mg tablets are bioequivalent to one 100 mg Arava tablet, the ANDAs cannot bear instructions to permit the use of five 20 mg tablets as an alternative to the Arava 100 mg tablet loading dose. Because the ANDA applicants do not have such data, the issue ultimately becomes whether they can carve out the loading dose that was a prerequisite to Arava approval. This question must be answered negatively.

Kali's argument that ANDA applicants need not seek approval of all dosage strengths of the reference product misses the point. Aventis does not contend that ANDA applicants must seek approval of a 100 mg leflunomide tablet. Rather, if a generic applicant does not seek approval of a 100 mg tablet, Aventis maintains that the

applicant must establish that five of its 20 mg tablets are bioequivalent to one 100 mg Arava tablet.[1] Otherwise, it may not label its product so as to permit the use of five 20 mg tablets as an alternative loading dose. The label would thus have to either omit the loading dose or reference a 100 mg tablet that the generic does not manufacture. Neither option should be permitted.

As set forth more fully in the original petition, omission of the loading dose would render the proposed generics not safe and effective. The loading dose is not the type of information that can be omitted from an ANDA label simply because the drug is manufactured by a different entity than the reference listed drug. 21 CFR § 314.94(a)(7), (a)(8)(iv); *see also* Draft Guidance for Industry: Referencing Discontinued Labeling for Listed Drugs in Abbreviated New Drug Applications (Oct. 2000). Thus, if the applicants do not intend to seek approval of a 100 mg tablet, FDA should require them to establish that 5 of their 20 mg tablets are bioequivalent to the 100 mg Arava tablet so that they may include this alternative loading dose regime. Without such a showing the ANDAs cannot be properly labeled.

The oxycodone hydrochloride extended-release tablets example Kali cites is inapposite. There, Teva obtained approval of only an 80 mg tablet. The reference drug, Oxycontin® (oxycodone HCl controlled-release) is available in 10 mg, 20 mg, 40 mg, 80 mg, and 160 mg tablets. Like the labeling of the reference drug Oxycontin, Teva's ANDA includes a statement that "[d]ose proportionality and/or bioavailability has been established for the 10 mg, 20 mg, 40 mg, 80 mg, and 160 mg tablet strengths for both peak plasma levels (C_{max}) and extent of absorption (AUC)." Here, in contrast, dose proportionality has not been established between the various dosage strengths. Indeed, FDA has itself said that bioequivalence data would be required in order for five 20 mg Arava tablets to be used interchangeably with a single 100 mg tablet. Without such data, then there is no basis for any ANDA holder with approval of only a 20 mg leflunomide tablet to include the requisite labeling for the 100 mg loading dose. Such an ANDA should not be approved.

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[1] To avoid the type of "Catch-22" situation Kali claims would arise if FDA required bioequivalence testing to the 100 mg tablet, Kali may seek sufficient 100 mg tablets for testing from Aventis.

Aventis appreciates this opportunity to respond to Kali's and Olsson's comments.

Respectfully submitted,

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